Journal of Cardiology (2009) **54**, 221—230

ELSEVIER

CARDIOLOGY
Official Journal of the Japanese College of Cardiology

www.elsevier.com/locate/jjcc

ORIGINAL ARTICLE

In patients with heart failure and non-ischemic heart disease, cardiac troponin T is a reliable predictor of long-term echocardiographic changes and adverse cardiac events

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Received 4 March 2009; received in revised form 23 April 2009; accepted 15 May 2009
Available online 18 June 2009

KEYWORDS
Heart failure;
Troponin;
Natriuretic peptide;
Remodeling;
Surrogate marker

Summary
Background: The relationships between (1) serum concentration of cardiac troponin T (cTnT) and clinical hemodynamic profiles, (2) cTnT versus B-type natriuretic peptide (BNP) and long-term echocardiographic changes, and (3) cTnT versus BNP and echocardiographic changes, and rates of adverse cardiac events, have not been well elucidated.
Methods: Retrospective analysis of 100 consecutive patients with heart failure, left ventricular ejection fraction <50%, and non-ischemic heart disease was performed.
Results: Baseline cTnT was ≥0.01 ng/ml in 30 patients. By multiple variable logistic regression analysis, diabetes mellitus [DM; odds ratio (OR) 7.5; $p = 0.014$], serum creatinine (OR 25.9; $p = 0.0157$), and pulmonary capillary wedge pressure (PCWP; OR 1.12; $p = 0.0214$) were independent predictors of baseline elevation of cTnT. At a follow-up of 40.6 ± 20.6 months, echocardiograms and cTnT and BNP measurements were available in 93 patients, of whom 23 experienced an adverse cardiac event. By multiple variable analyses, elevated cTnT at follow-up was negatively correlated with echocardiographic improvements in cardiac function (OR 0.10; $p = 0.019$), and

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0914-5087/$ — see front matter
doi:10.1016/j.jjcc.2009.05.007

was a significant predictor of adverse cardiac events after adjustment for covariables, including follow-up BNP and echocardiographic changes (hazard ratio 5.6; $p = 0.0046$). *Conclusions:* DM, serum creatinine, and PCWP were correlated with elevated baseline serum cTnT concentrations. cTnT concentration during follow-up might be a surrogate marker of heart failure.

Introduction

The blood concentrations of B-type natriuretic peptide (BNP) are used as a marker of myocardial load, and several studies have examined their diagnostic and predictive value in patients suffering from heart failure (HF) [1,2]. Moreover, the changes in BNP that take place over time have been correlated with long-term risk of adverse cardiac events [3,4] and changes in cardiac function ascertained by echocardiography [5,6]. On the other hand, the serum concentrations of cardiac troponin (cTn) T [7], a marker of myocyte injury, can be used to risk stratify patients presenting with chronic [8—13] or acute congestive HF [14,15]. However, the relationships between serum cTnT concentrations and (1) clinical characteristics and measurements made during baseline cardiac catheterization, (2) long-term changes in echocardiographic cardiac function with BNP concentrations as one of the confounding variables, and (3) long-term clinical outcomes with BNP concentrations and echocardiographic changes as the confounding variables, have not been studied in depth.

Patients and methods

Between January 2001 and June 2007, we searched our database of elective diagnostic cardiac catheterization, and identified 100 consecutive patients who had a <50% left ventricular (LV) ejection fraction (EF) on ventriculography, in absence of (a) history of myocardial infarction and (b) >50% stenosis of any coronary artery. Patients with congenital heart disease, aortic valve disease, mitral valve regurgitation requiring surgical treatment, history of myocarditis, malignancy, connective tissue disease or cardiac amyloidosis, and patients undergoing hemodialysis were excluded from this analysis. All study procedures were in compliance with the institutional guidelines of Hyogo Prefectural Amagasaki Hospital.

Baseline data collection

In this retrospective analysis of a database of patients with HF and non-ischemic heart disease accumulated since 1995 [7—9], baseline concentrations of cTnT (3rd generation assays, Roche Diagnostics, Mannheim, Germany) and BNP (Shionogi & Co., Ltd., Osaka, Japan) were measured in blood samples collected during hospitalization within 2 months before the diagnostic cardiac catheterization procedure in all 100 patients. A cTnT serum concentration $\geq$0.01 ng/ml was classified as elevated, since it is <0.01 ng/ml in 99th percentile of healthy subjects [12,16]. LVEF calculated by Simpson's modified method, and LV end-diastolic diameter (EDD) were measured echocardiographically. Diabetes mellitus (DM) was defined as a fasting serum glucose $\geq$126 mg/dl, non-fasting serum glucose >200 mg/dl, or use of an anti-diabetic medication. Hypertension was defined as a resting systolic blood pressure $\geq$140 mmHg, or diastolic blood pressure $\geq$90 mmHg, or use of an antihypertensive medication. Hypercholesterolemia was defined as a total cholesterol $\geq$240 mg/dl, or use of a statin.

Follow-up data collection and definition of adverse cardiac events

The patients were followed until March 2008. The latest available echocardiographic measurements and cTnT and BNP serum concentrations were used as follow-up data. The echocardiographic change was classified as improved when (1) LVEF had increased by $\geq$5% and (2) LVEDD had decreased by $\geq$5 mm from baseline. Adverse cardiac events included sudden death, death from HF, and re-hospitalization for management of cardiac decompensation with pulmonary edema and orthopnea, requiring the emergent administration of intravenous diuretics, inotropes, or vasodilators.

Statistical analysis

All results are presented as means $\pm$ standard deviation (S.D.). Continuous variables were compared by factorial analysis of variance, and dichotomous variables by Chi-square analysis. A logistic regression analysis was performed to examine the relationship between (1) elevated cTnT and baseline characteristics, and (2) changes in

echocardiographic cardiac function and clinical variables including cTnT and BNP concentrations. Odds ratios and 95% confidence intervals were calculated. Adverse cardiac event-free survival curves were constructed by the Kaplan—Meier method, and compared by log—rank test. Cox regression analysis was used to evaluate the prognostic value of each variable. Hazard ratios and 95% confidence intervals were calculated. Variables that were significant in the single variable analysis were included in the multiple variable models, and a stepwise forward multiple variable analysis was carried out to identify independent correlations. A p value <0.05 was considered significant. The JMP® for Windows statistical package, Version 5.1 (SAS Institute Inc., Cary, NC, USA) was used for all analyses.

Results

Baseline characteristics and cTnT concentrations

Among the 100 patients included in this analysis, 30 (30%) had a serum cTnT concentration ≥0.01 ng/ml. Compared with patients whose baseline cTnT concentration was <0.01 ng/ml, patients with elevated cTnT (a) were in a significantly higher mean New York Heart Association (NYHA) functional class, (b) had a lower mean hemoglobin, (c) had higher serum creatinine and BNP concentrations, and higher pulmonary capillary wedge pressure (PCWP) at the time of diagnostic catheterization, and (d) were significantly more likely to be diabetic (Table 1).

The variables listed in Table 1 were tested by logistic regression analysis in search of correlates of elevated cTnT (Table 2). NYHA functional class and a history of DM, as dichotomous variables, and hemoglobin, creatinine, PCWP and BNP concentration, as continuous variables, were correlated with serum cTnT concentrations at baseline. By unadjusted and adjusted multiple variable analysis, a history of DM, serum creatinine concentration, and PCWP were independent predictors of baseline cTnT.

Echocardiographic changes in cardiac function and follow-up cTnT versus follow-up BNP measurements

Out of the 100 consecutive patients, 7 were lost to follow-up and contributed no data to this analysis. The latest echocardiographic observations in the 93 remaining patients were made at a mean follow-up of 33.0 ± 18.4 months, and the latest measurements of serum cTnT and BNP concentrations at 37.6 ± 21.4 months. A ≥5% increase in LVEF was observed in 72 patients, a ≥5 mm decrease in LVEDD was observed in 53 patients, and both were observed in 52 patients. A logistic regression analysis was performed in search of correlates of improvements, in echocardiographic cardiac function, including all variables listed in Table 1, and the follow-up measurements of cTnT and BNP. By single variable analysis, the long-term echocardiographic improvements, were correlated with (a) diagnosis of HF for >1 year, (b) follow-up cTnT and BNP serum concentrations, and (c) use of a beta-adrenergic blocker during follow-up (Table 3), though were correlated with baseline measurements of neither cTnT ($p = 0.922$) nor BNP ($p = 0.121$) concentrations. By unadjusted multiple variable analysis, follow-up concentrations of cTnT and BNP were independent predictors of echocardiographic improvements; however, after adjustment for covariables, follow-up cTnT concentration emerged as the single independent predictor (Table 3).

Adverse cardiac event-free rate and follow-up cTnT versus follow-up BNP and echocardiographic improvement in cardiac function

During a follow-up of 40.6 ± 20.6 months, 23 adverse cardiac events occurred, including 5 deaths due to HF, and 1 sudden death. Kaplan—Meier survival curves were constructed according to the baseline and follow-up measurements of cTnT and BNP. Patients whose initial BNP concentration was above versus below the median value of 460 pg/ml had similar adverse cardiac event-free survivals (Fig. 1A). In contrast, patients whose follow-up BNP concentration was above the median value of 65.4 pg/ml had a significantly lower adverse cardiac event-free survival than patients whose follow-up BNP concentration was ≤65.4 pg/ml (Fig. 1B). Patients whose serum cTnT concentration was <0.01 ng/ml at baseline (Fig. 2A) or during long-term follow-up (Fig. 2B) had a significantly higher adverse cardiac event-free survival than patients whose cTnT concentration was ≥0.01 ng/ml.

By single variable Cox regression analysis, NYHA functional class III or IV, old age, a history of HF for >1 year, and elevated follow-up cTnT and BNP concentrations were positive predictors, whereas an echocardiographic improvement in cardiac function was a negative predictor of adverse cardiac events (Table 4). By multiple variable analyses, follow-up cTnT and BNP serum concentrations were independent predictors of adverse cardiac

Table 1 Patient characteristics and baseline cardiac troponin T (cTnT).

	All patients ($n=100$)	Baseline cTnT		p^a
		≥0.01 ($n=30$)	<0.01 ($n=70$)	
Age, years	60.7 ± 12.3	61.9 ± 13.2	60.2 ± 11.9	0.533
Women/men	36/64	11/19	25/45	0.999
NYHA functional class I+II	45/100	6/30	39/70	0.001
Height, cm	160.4 ± 8.9	160.4 ± 10.1	160.4 ± 8.5	0.975
Body weight, kg	60.8 ± 15.4	61.6 ± 17.1	60.5 ± 14.7	0.751
Atrial fibrillation at baseline	39/100	8/30	31/70	0.120
History of				
Hypertension	47/100	13/30	34/70	0.667
Hyperlipidemia	15/100	5/30	10/70	0.765
Diabetes mellitus	17/100	9/30	8/70	0.039
Heart failure for >1 year	27/100	11/30	16/70	0.218
Hemoglobin, g/dl	13.9 ± 1.8	13.3 ± 2.1	14.1 ± 1.7	0.037
Serum creatinine, mg/dl	0.97 ± 0.31	1.14 ± 0.41	0.89 ± 0.22	0.0003
Cholesterol, mg/dl	185 ± 37	178 ± 38	188 ± 36	0.180
B-type natriuretic peptide, pg/ml	594 ± 615	875 ± 813	474 ± 463	0.002
Catheterization procedure				
Aortic blood pressure, mmHg				
Systolic	127 ± 24	125 ± 20	128 ± 26	0.558
Diastolic	75 ± 14	72 ± 12	76 ± 15	0.218
Heart rate, bpm	83 ± 17	81 ± 12	84 ± 19	0.530
Left ventricular ejection fraction, %	32.6 ± 10.5	29.5 ± 11.2	33.9 ± 10.0	0.054
Pulmonary capillary wedge pressure, mmHg	11.4 ± 7.3	15.4 ± 8.4	9.7 ± 6.0	0.0003
Cardiac index, l/min per m^2	3.0 ± 0.8	2.9 ± 0.9	3.0 ± 0.7	0.490
Echocardiographic measurements				
Left ventricular ejection fraction, %	35.1 ± 8.9	34.0 ± 9.2	35.5 ± 8.9	0.454
Left ventricular diastolic diameter, mm	60.9 ± 6.8	62.8 ± 7.1	60.2 ± 6.6	0.084
Medications during follow-up				
ACE inhibitor, ARB	83/100	26/30	57/70	0.576
Beta-adrenergic blocker	76/100	23/30	53/70	0.999

Values are means ± S.D. or numbers of observations. NYHA, New York Heart Association; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

[a] ≥0.01 ng/ml versus <0.01 ng/ml baseline cTnT concentration.

events. However, after adjustment for covariables, including echocardiographic improvement in cardiac function, BNP was no longer predictive, and follow-up cTnT concentration remained as a single independent predictor of adverse cardiac events.

Discussion

Alterations in the biology of cardiac myocytes is the primary event that initiates the process of cardiac remodeling, itself believed to be a major surrogate marker for adverse cardiac events in patients with HF [17—20]. This study retrospectively examined the correlation between elevated serum cTnT concentrations and (a) baseline patient characteristics and hemodynamic measurements made during baseline cardiac catheterization, (b) long-term changes in echocardiographic cardiac function with BNP concentrations, and (c) long-term rates of adverse cardiac events with BNP concentrations and echocardiographic changes. Since coronary artery stenoses may increase the serum concentration of cTnT and coronary interventions may influence the echocardiographic changes that take place over time, patients with ischemic heart disease were excluded from this analysis.

Baseline characteristics and cTnT

The clinical and hemodynamic factors that are associated with elevated baseline cTnT concentrations were previously unknown. This analysis revealed that a history of DM, an elevated serum creatinine,

Table 2 Correlates of elevated baseline serum cardiac troponin T (cTnT) in single and multiple variable logistic regression analysis.

	Analysis			
	Single variable	Multiple variable		
		Unadjusted	Adjusted[a]	Adjusted[b]
NYHA functional class I or II	0.19 (0.07—0.54) $p = 0.0017$	$p = 0.080$	$p = 0.076$	-
History of diabetes mellitus	3.3 (1.1—9.7) $p = 0.0284$	4.2 (1.1—16.5) $p = 0.035$	5.6 (1.3—23.5) $p = 0.0189$	7.5 (1.5—37.7) $p = 0.014$
Hemoglobin (g/dl)	0.77 (0.60—0.99) $p = 0.0446$	$p = 0.057$	$p = 0.108$	—
Serum creatinine (mg/dl)	13.9 (2.8—69.4) $p = 0.0013$	12.9 (1.9—88.0) $p = 0.0087$	22.1 (2.4—204.9) $p = 0.0063$	25.9 (1.8—364.9) $p = 0.0157$
Pulmonary capillary wedge pressure, mmHg	1.12 (1.04—1.20) $p = 0.0017$	1.10 (1.01—1.19) $p = 0.023$	1.09 (1.01—1.19) $p = 0.022$	1.12 (1.01—1.23) $p = 0.0214$
B-type natriuretic peptide, pg/ml	1.001 (1.000—1.002) $p = 0.0077$	—	—	—

Values are odds ratios (95% confidence intervals).

[a] For age, gender.

[b] For age, gender, height, body weight, atrial fibrillation, left ventricular ejection fraction, hemoglobin, and New York Heart Association (NYHA) functional class.

Table 3 Factors correlated with echocardiographic improvements in cardiac function during long-term follow-up.

	Analysis			
	Single variable	Multiple variable		
		Unadjusted	Adjusted[a]	Adjusted[b]
History of heart failure >1 year	0.37 (0.14—0.94) $p = 0.037$	—	—	—
Follow-up cTnT $\geq$0.01, ng/ml	0.08 (0.01—0.41) $p = 0.0021$	0.15 (0.02—0.79) $p = 0.0255$	0.16 (0.03—0.87) $p = 0.0343$	0.10 (0.01—0.68) $p = 0.019$
Follow-up BNP >median value (65.4 pg/ml)	0.21 (0.09—0.53) $p = 0.0007$	0.32 (0.12—0.85) $p = 0.0222$	$p = 0.106$	$p = 0.090$
Use of beta-adrenergic blocker	3.09 (1.09—8.71) $p = 0.0324$	$p = 0.0781$	$p = 0.077$	—

Values are odds ratios (95% confidence intervals). cTnT, cardiac troponin T; BNP, B-type natriuretic peptide.

[a] For age and gender.

[b] For age, gender, hemoglobin, serum creatinine, left ventricular ejection fraction, New York Heart Association (NYHA) functional class, pulmonary capillary wedge pressure, history of heart failure, and use of beta-adrenergic blocker, angiotensin-converting enzyme inhibitor, and angiotensin receptor blocker.

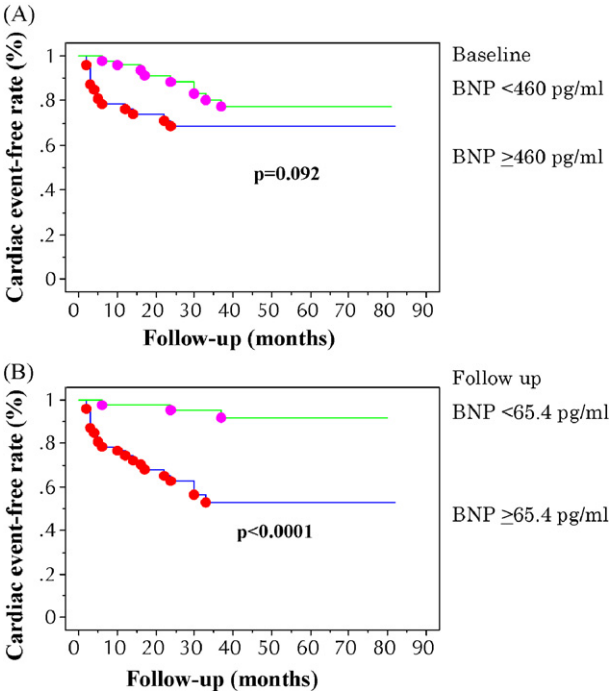

Figure 1 (A) Adverse cardiac event-free survivals according to baseline serum B-type natriuretic peptide (BNP) concentration <460 pg/ml ($n = 46$) versus ≥460 pg/ml ($n = 47$). (B) Adverse cardiac event-free survivals according to last serum BNP concentration <65.4 pg/ml ($n = 46$) versus ≥65.4 pg/ml ($n = 47$).

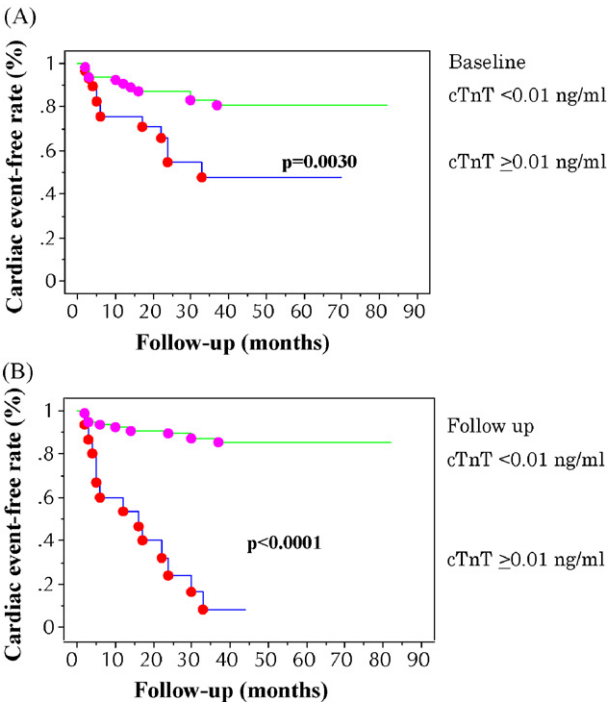

Figure 2 (A) Adverse cardiac event-free survivals according to baseline serum cardiac troponin T (cTnT) concentration <0.01 ng/ml ($n = 64$) versus ≥0.01 ng/ml ($n = 29$). (B) Adverse cardiac event-free survivals according to last serum cTnT concentration <0.01 ng/ml ($n = 78$) versus ≥0.01 ng/ml ($n = 15$).

and elevated PCWP were independent predictors of elevated cTnT after adjustment for several confounding variables. Our previous analysis of 2 other databases showed no correlation between baseline concentrations of cTnT and LVEF [9,21]. Similarly, Horwich et al. observed no correlation between elevated concentrations of cTnI and baseline LVEF; though found a correlation with PCWP [10]. Also in support of our observations, Wallace et al. reported the results of a multiple variable logistic regression analysis, which revealed that LV hypertrophy, HF, DM, and chronic kidney disease were independently associated with elevated cTnT in the general population [22].

The mechanism(s) of cTnT release in patients with HF remains unclear. We and other investigators have previously found correlations between elevated serum cTnT and elevated BNP, renin, norepinephrine, and C-reactive protein serum concentration, suggesting that myocardial load, activation of the rennin—angiotensin—aldosterone and autonomic sympathetic systems, and inflammation are causes of myocyte injury in patients with chronic HF [12,21]. In patients with acutely decompensated HF, hypotension upon admission to the hospital and the administration of intravenous inotropes may also cause further increases in cTnT [23,24]. In this analysis, however, renin, norepinephrine, and C-reactive protein measurements were not available.

While the mechanisms of cTnT elevation in patients with renal insufficiency are also unresolved, elevation of cTnT in this clinical setting has prognostic implications [25]. A recent study found that cTnT is fragmented into molecules small enough to be excreted by the kidney [26]. Therefore, the serum concentrations of cTnT might be partially determined by renal clearance. Moreover, DM increases the risk of HF regardless of the presence or absence of underlying coronary artery disease, and may be a cause of cardiomyopathy [27]. Meticulous attention to these background factors might be important therapeutic goals, with a view to lower serum cTnT concentrations and attenuate myocyte injury associated with cardiac remodeling.

Improvements in echocardiographic cardiac function and follow-up cTnT versus BNP measurements

We have hypothesized that elevated serum concentrations of cTnT are a marker of myocyte injury

Table 4 Factors correlated with adverse cardiac events during long-term follow-up.

	Analysis				
	Single variable	Multiple variable			
		Unadjusted	Adjusted[a]	Adjusted[b]	Adjusted[c]
NYHA functional class III or IV at baseline	3.2 (1.2—8.7) $p = 0.019$	—	—	—	—
Age	1.06 (1.02—1.11) $p = 0.002$	—	—	—	—
History of heart failure >1 year	3.15 (1.38—7.15) $p = 0.006$	—	—	—	—
Echocardiographic changes	0.12 (0.04—0.37) $p = 0.0002$	—	—	—	—
Follow-up cTnT $\geq$0.01 ng/ml	11.4 (4.9—26.9) $p < 0.0001$	7.1 (2.8—17.6) $p < 0.0001$	6.4 (2.5—16.5) $p < 0.0001$	7.9 (2.5—24.8) $p = 0.0004$	5.6 (1.7—18.4) $p = 0.0046$
Follow-up BNP >65.4 pg/ml	8.3 (2.4—28.0) $p = 0.0006$	4.6 (1.2—16.8) $p = 0.0183$	3.9 (1.04—14.6) $p = 0.042$	4.9 (1.04—23.7) $p = 0.043$	$p = 0.103$

Values are hazard ratios (95% confidence intervals). cTnT, cardiac troponin T; BNP, B-type natriuretic peptide.

[a] For age and gender.

[b] For age, gender, hemoglobin, serum creatinine, left ventricular ejection fraction, New York Heart Association (NYHA) functional class, pulmonary capillary wedge pressure, history of heart failure, and use of beta-adrenergic blocker, angiotensin-converting enzyme inhibitor, and angiotensin receptor blocker.

[c] For all covariables listed under b improvements in echocardiography.

[7], and studies performed by us and by others have found a negative correlation between cTnT elevation and long-term echocardiographic improvements in cardiac function [9—11]. However, no study has compared the correlation between echocardiographic changes and elevated cTnT versus elevated BNP concentrations. On the other hand, a correlation has been reported between long-term changes in BNP and long-term echocardiographic changes in cardiac function [5,6]. In this study, follow-up cTnT and BNP concentrations were both independently associated with echocardiographic changes. However, after adjustments for confounding variables, follow-up cTnT emerged as the only significant predictor. It has been reported that the combination measurement of both cTnT and BNP can identify patients at highest risk [2,7,10,15,28,29]. In this study, the odds ratio of both elevated cTnT and BNP at follow-up for the echocardiographic change was the lowest [unadjusted: 0.042 (0.005—0.340), $p = 0.0029$; adjusted by confounding variables listed in Table 3: 0.031 (0.003—0.366), $p = 0.0058$].

Adverse cardiac event-free rate and follow-up cTnT versus BNP and improvements in echocardiographic cardiac function

Before the use of BNP, improvements in echocardiographic measurements of cardiac function over time were considered a surrogate marker of adverse cardiac events [19]. BNP is now widely used for the diagnosis and risk stratification of HF [1,2] and, since changes in BNP over time correlate with rates of adverse cardiac events [3,4], it is considered a surrogate marker of such events. Furthermore, both cTnT and BNP are independent predictors of adverse cardiac events in patients suffering from HF [2,7,10,15,28,29]. However, the predictive power of follow-up measurements of cTnT has not been compared with that of follow-up measurement of BNP or long-term improvements in echocardiographic cardiac function. In this study, follow-up cTnT, follow-up BNP concentrations, and echocardiographic changes were significantly correlated with long-term rates of adverse cardiac events in the single variable analysis, and follow-up cTnT and BNP concentrations were both independent predictors of adverse cardiac events in the multiple variable analysis. However, after adjustment for covariables, including echocardiographic improvement in cardiac function, BNP was no longer predictive, and follow-up cTnT concentration remained as a single independent predictor of adverse cardiac events. The hazard ratio of both elevated cTnT and BNP at follow-up was the highest [unadjusted: 14.5 (6.0—35.1), $p < 0.0001$; adjusted by confounding variables listed in Table 4: 7.6 (2.2—25.7), $p = 0.0010$].

In conclusion, in patients with HF and non-ischemic heart disease, follow-up cTnT was a powerful predictor of changes in echocardiographic cardiac function and adverse cardiac events. Therefore, serial measurements of cTnT might be a powerful surrogate marker of HF.

Study limitations

This study was conducted at a single institution and included a relatively small patient population. Therefore, creatinine was not a significant predictor of echocardiographic change and long-term prognosis. Furthermore, since our analysis, based on a diagnostic catheterization database, was retrospective, the timing of serial echocardiographic observations and measurements of cTnT and BNP was not systematically planned, and no attempt was made to examine the effects of therapy. Although echocardiographic parameters such as E/A and Tei index are powerful prognostic indicators [30—32], these parameters were not available. Finally, cTnT was treated as a dichotomous variable because the 3rd generation assay cannot measure concentrations <0.01 ng/ml. However, the upcoming, highly sensitive, next-generation cTnT assay [12,33] will enable the measurement of risk as a cTnT concentration-dependent factor, and examine the influence of proportional changes in cTnT on echocardiographic changes and adverse cardiac events.

Acknowledgment

We thank Rodolphe Ruffy, MD (www.cardioscript.com) for editing the manuscript.

References

[1] de Lemos JA, McGuire DK, Drazner MH. B-type natriuretic peptide in cardiovascular disease. Lancet 2003;362:316—22.

[2] Tang WH, Francis GS, Morrow DA, Newby LK, Cannon CP, Jesse RL, Storrow AB, Christenson RH, Apple FS, Ravkilde J, Wu AH. National Academy of Clinical Biochemistry Laboratory Medicine. National Academy of Clinical Biochemistry Laboratory Medicine practice guidelines: clinical utilization of cardiac biomarker testing in heart failure. Circulation 2007;116:e99—e109.

[3] Anand IS, Fisher LD, Chiang YT, Latini R, Masson S, Maggioni AP, Glazer RD, Tognoni G, Cohn JN, Val-HeFT Investigators. Changes in brain natriuretic peptide and norepinephrine over time and mortality and morbidity in the Valsartan Heart Failure Trial. Circulation 2003;107: 1278—83.
[4] Bettencourt P, Azevedo A, Pimenta J, Frioes F, Ferreira S, Ferreira A. N-terminal-pro-brain natriuretic peptide predicts outcome after hospital discharge in heart failure patients. Circulation 2004;110:2168—74.
[5] Latini R, Masson S, Wong M, Barlera S, Carretta E, Staszewsky L, Vago T, Maggioni AP, Anand IS, Tan LB, Tognoni G, Cohn JN, Val-HeFT Investigators. Incremental prognostic value of changes in B-type natriuretic peptide in heart failure. Am J Med 2006;119:e23—e30.
[6] Yan RT, White M, Yan AT, Yusuf S, Rouleau JL, Maggioni AP, Hall C, Latini R, Afzal R, Floras J, Masson S, McKelvie RS. Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) Investigators. Usefulness of temporal changes in neurohormones as markers of ventricular remodeling and prognosis in patients with left ventricular systolic dysfunction and heart failure receiving either candesartan or enalapril or both. Am J Cardiol 2005;96:698—704.
[7] Sato Y, Kita T, Takatsu Y, Kimura T. Biochemical markers of myocyte injury in heart failure. Heart 2004;90: 1110—3.
[8] Sato Y, Kataoka K, Matsumori A, Sasayama S, Yamada T, Ito H, Takatsu Y. Measuring serum aminoterminal type III procollagen peptide, 7S domain of type IV collagen, and cardiac troponin T in patients with idiopathic dilated cardiomyopathy and secondary cardiomyopathy. Heart 1997;78: 505—8.
[9] Sato Y, Yamada T, Taniguchi R, Nagai K, Makiyama T, Okada H, Kataoka K, Ito H, Matsumori A, Sasayama S, Takatsu Y. Persistently increased serum concentrations of cardiac troponin T in patients with idiopathic dilated cardiomyopathy are predictive of adverse outcomes. Circulation 2001;103:369—74.
[10] Horwich TB, Patel J, MacLellan WR, Fonarow GC. Cardiac troponin I is associated with impaired hemodynamics, progressive left ventricular dysfunction, and increased mortality rates in advanced heart failure. Circulation 2003;108:833—8.
[11] Perna ER, Macin SM, Canella JP, Augier N, Stival JL, Cialzeta JR, Pitzus AE, Garcia EH, Obregón R, Brizuela M, Barbagelata A. Ongoing myocardial injury in stable severe heart failure: value of cardiac troponin T monitoring for high-risk patient identification. Circulation 2004;110: 2376—82.
[12] Latini R, Masson S, Anand IS, Missov E, Carlson M, Vago T, Angelici L, Barlera S, Parrinello G, Maggioni AP, Tognoni G, Cohn JN, Val-HeFT Investigators. Prognostic value of very low plasma concentrations of troponin T in patients with stable chronic heart failure. Circulation 2007;116: 1242—9.
[13] Miller WL, Hartman KA, Burritt MF, Grill DE, Rodeheffer RJ, Burnett Jr JC, Jaffe AS. Serial biomarker measurements in ambulatory patients with chronic heart failure. The importance of change over time. Circulation 2007;116: 249—57.
[14] Peacock 4th WF, De Marco T, Fonarow GC, Diercks D, Wynne J, Apple FS, Wu AH. ADHERE Investigators. Cardiac troponin and outcome in acute heart failure. N Engl J Med 2008;358:2117—26.
[15] Sakhuja R, Green S, Oestreicher EM, Sluss PM, Lee-Lewandrowski E, Lewandrowski KB, Januzzi Jr JL. Amino-terminal pro-brain natriuretic peptide, brain natriuretic peptide, and troponin T for prediction of mortality in acute heart failure. Clin Chem 2007;53:412—20.
[16] Morrow DA, Cannon CP, Jesse RL, Newby LK, Ravkilde J, Storrow AB, Wu AH, Christenson RH. National Academy of Clinical Biochemistry. National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines: clinical characteristics and utilization of biochemical markers in acute coronary syndromes. Circulation 2007;115: e356—75.
[17] Mann D, Bristow MR. Mechanisms and models in heart failure: the biomechanical model and beyond. Circulation 2005;111:2837—49.
[18] Cohn JN, Ferrari R, Sharpe N. Cardiac remodelling—concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. Behalf of an International Forum on Cardiac Remodeling. J Am Coll Cardiol 2000;35:569—82.
[19] Anand IS, Florea VG, Fisher L. Surrogate end points in heart failure. J Am Coll Cardiol 2002;39:1414—21.
[20] Wong M, Staszewsky L, Latini R, Barlera S, Glazer R, Aknay N, Hester A, Anand I, Cohn JN. Severity of left ventricular remodeling defines outcomes and response to therapy in heart failure: Valsartan heart failure trial (Val-HeFT) echocardiographic data. J Am Coll Cardiol 2004;43: 2022—7.
[21] Nishio Y, Sato Y, Taniguchi R, Shizuta S, Doi T, Morimoto T, Kimura T, Kita T. Cardiac troponin T vs. other biochemical markers in patients with congestive heart failure. Circ J 2007;71:631—5.
[22] Wallace TW, Abdullah SM, Drazner MH, Das SR, Khera A, McGuire DK, Wians F, Sabatine MS, Morrow DA, de Lemos JA. Prevalence and determinants of troponin T elevation in the general population. Circulation 2006;113: 1958—65.
[23] Kuwabara Y, Sato Y, Miyamoto T, Taniguchi R, Matsuoka T, Isoda K, Yamane K, Nishi K, Fujiwara H, Takatsu Y. Persistently increased serum concentrations of cardiac troponin in patients with acutely decompensated heart failure are predictive of adverse outcomes. Circ J 2007;71: 1047—51.
[24] Sato Y, Kuwabara Y, Taniguchi R, Nishio Y, Miyamoto T, Fujiwara H, Takatsu Y. Malignant link between chronic heart failure and acute cardiac decompensation in patients with persistently increased serum concentrations of cardiac troponin. Int J Cardiol 2008;126:171—6.
[25] Khan NA, Hemmelgarn BR, Tonelli M, Thompson CR, Levin A. Prognostic value of troponin T and I among asymptomatic patients with end-stage renal disease: a meta-analysis. Circulation 2005;112:3088—96.
[26] Diris JH, Hackeng CM, Kooman JP, Pinto YM, Hermens WT, van Dieijen-Visser MP. Impaired renal clearance explains elevated troponin T fragments in hemodialysis patients. Circulation 2004;109:23—5.
[27] Boudina S, Abel ED. Diabetic cardiomyopathy revisited. Circulation 2007;115:3213—23.
[28] Taniguchi R, Sato Y, Yamada T, Ooba M, Higuchi H, Matsumori A, Kimura T, Kita T. Combined measurements of cardiac troponin T and N-terminal pro-brain natriuretic peptide in patients with heart failure. Circ J 2004;68:1160—4.
[29] Taniguchi R, Sato Y, Nishio Y, Kimura T, Kita T. Measurements of baseline and follow-up concentrations of cardiac troponin-T and brain natriuretic peptide in patients with heart failure from various etiologies. Heart Vessels 2006;21:344—9.
[30] Seo Y, Ishizu T, Kawano S, Watanabe S, Ishimitsu T, Aonuma K. Combined approach with Doppler echocardiography

and B-type natriuretic peptide to stratify prognosis of patients with decompensated systolic heart failure. J Cardiol 2008;52:224—31.
[31] Kirkpatrick JN, Vannan MA, Narula J, Lang RM. Echocardiography in heart failure: applications, utility, and new horizons. J Am Coll Cardiol 2007;50:381—96.
[32] Dujardin KS, Tei C, Yeo TC, Hodge DO, Rossi A, Seward JB. Prognostic value of a Doppler index combining systolic and diastolic performance in idiopathic-dilated cardiomyopathy. Am J Cardiol 1998;82:1071—6.
[33] Sato Y, Miyamoto T, Taniguchi R, Nagao K, Matsuoka T, Fukuhara R, Kuwabara Y, Isoda K, Yamane K, Nishi K, Saijyo S, Fujiwara H, Takatsu Y. The clinical and hemodynamic factors that influence the concentrations of biomarkers of myocyte injury measured by high sensitive assay PATHFAST. J Cardiol 2009;53:20—7.